THE COUNCIL FOR TOBACCO RESEARCH – U.S.A., INC.

September 17, 1974

To: The Scientific Advisory Board

Subject: Renewal Request: Mouse Model System for In Vivo Lung Carcinogenesis
CTR Contract #2 (MA #2220)

This pilot project is designed to further define a mouse carcinogenic model system which can be used for further inhalation studies. Some promising leads have been confirmed, i.e., that squamous cell carcinoma can be induced in an AHH inducible mouse, following intratracheal injection of M.C.A.

The experiment #5 designed to elucidate the relationship between sensitivity to intratracheally instilled M.C.A. induced squamous cell carcinomas and inducibility of AHH is currently being repeated (CTR #39) using the C_3H and DBA lines and appropriate crosses. This cross mimics the autosomal codominant relationship reported by Shaw in humans. The original study (CTR #5) using the $C_{57}Bl6$ X DBA_2 cross was not effective in inducing significant numbers of squamous cell carcinomas, possibly due to small particle size.

Particle size, or chemical residence time in the lung, may also explain why an M.C.A. dose in a gelatin vehicle is much more lethal than M.C.A. in a treoctanoine carrier (CTR 3A, 3B) and more carcinogenic (CTR 3A, 3B, 3C) in AHH inducible mice.

An additional study to be initiated within the next few weeks is a study of vitamin A in carcinogenesis, with squamouse cell carcinoma of the lung as an end point.

The studies proposed using dioxime (TCDD) as an inducer of all types of AHH enzymes (constituitive and induced), and the studies of AHH competitive inhibitors and their effects on M.C.A. induced lung tumors are directed to answering questions concerning chronicity of exposure to AHH inducers (such as is the case of a heavy smoker) and potentiation of lung tumorigenesis. Preliminary evidence of optimal tumor production conditions points to a necessity for concurrent exposure to AHH inducer and carcinogen. This must be repeated and documented. Inhibition studies at various steps in the metabolic breakdown of a polycyclic aromatic hydrocarbon should help to further elucidate the mechanism of carcinogenesis by PAH chemical carcinogens.

Smoke condensate dissolved in beeswax pellets and implanted S.C. resulted in insignificant tumors. However, tumors were readily

produced when 10 mg M.C.A. (normally below the tumor breakthrough level) plus smoke condensate fractions were mixed in a beeswax pellet. Further work including subfractionations will be required to show the mode of action of specific fractions, whether as enzyme inducers, DNA repair inhibitors or other.

An experiment has been added to the list after the August 19 deadline. This experiment is a criticallt important dosimetry study to show the lowest levels of M.C.A. and BP which, if instilled, can produce tumors. This must precede inhalation studies with smoke as cocarcinogen.

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